DEVELOPMENT OF A PERCUTANEOUS ACCESS DEVICE

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The Surgical Research Laboratory at Sinai Hospital of Detroit has been involved in the study of percutaneous access devices for a number of years. An underlying problem has compromised past attempts to implant a foreign body through the skin. There is a natural propensity for the epidermis to close unnatural openings by proliferating and migrating until continuity has been restored. The result of this process is marsupialization of the implant or sinus-tract formation when marsupialization is incomplete[1,2]. Attempts to deal with this problem have, in the past, involved such approaches as the utilization of materials intended to "deceive" the epidermal cells, resulting in the acceptance of the material as a natural end point to cell migration. Thus far, none of the numerous materials tested have been effective in this regard.

The overall objective of this research is the development of a percutaneous access device (PAD) which satisfies long-term performance criteria while maintaining freedom from infection, extrusion, and marsupialization. It is our hypothesis that a) control of epidermal cell proliferation, and b) protection of the tissue-implant seal from mechanical stresses will result in a PAD having the desired characteristics. Observations of related investigations point to the fact that a strong bond between the implant and surrounding tissue must be formed in order to prevent sinus-tract development with ensuing microbial infection[1,3]. Three principal techniques are being used to accomplish our objective.

First, basal cells of the epidermis proliferate on but not through the dermis. It is believed that they are prevented from doing so by the presence of the collagenous network which constitutes a major portion of the dermis[4]. Therefore, we believe that epidermal downgrowth may be inhibited if a percutaneous implant is precoated with autologous dermal fibroblasts which have formed a collagenous matrix firmly interlocked with a porous implant surface (Figure 1). This is accomplished in vitro using cell culture techniques under conditions that favor fibroblast proliferation followed by collagen synthesis and polymerization.

Second, during surgical implantation of the PAD, the epidermis is removed from the region surrounding the PAD neck. This prevents the epidermis from migrating down the wound before firm attachment of the native dermis to the collagen and fibroblast coated, porous surface takes place. After approximately 2 wks, basal cells are allowed to proliferate over the dermis but should be prevented from channeling inward along the PAD by the interlocking of the collagenous network with the porous implant surface.

Third, since the PAD will be subject to varying loads which tend to mechanically separate the tissue-implant bond, it is necessary to stabilize the PAD and protect the PAD-tissue interface from loads which exceed the strength of this bond. This is accomplished through the use of a large flange which is implanted subcutaneously, after removing the hypodermis, and is integral with the PAD neck (Figure 2). The PAD prototypes which are being examined are designed for implantation in soft tissue.

METHODS

Relief of Mechanical Stress. To evaluate the ability of a subcutaneously implanted flange to redistribute strain in the skin, 24 implantations in 6 miniature Yucatan pigs were carried out. Since this part of our experiment was designed solely for quantitating strain distribution, dacron velour covered discs without any percutaneous parts were used. Four implant sizes were evaluated, 5.5, 7, 8.5 and 10 cm in diameter. The implants were placed in a pocket created subcutaneously after most of the hypodermis from this location was removed. Four pockets per animal were created, 3 of them received 3 different sizes of implants and the fourth without any implant was used as control. A grid was tattooed on the skin over the implants to provide landmarks enabling measurement of strain.

After the wound healed, a pneumatically operated device was temporarily glued to the skin over the implants at weekly intervals and was used to stretch as well as compress the skin approximately 15%. Photographs were taken in all 3 positions (Figure 3), then these photographs were digitized, fed into a computer which calculated and plotted the strain vs position curve for each implant and control (Figures 4-6).

Creating the Porous Surface. The purpose of a porous surface is to allow ingrowth (polymerization) of collagen fibers, thus establishing a barrier to epidermal cell migration. To discourage bacterial contamination, the pore diameter selected was 500 nm or less. For this reason, this surface is referred to as the "nanoporous" surface. A list of experimental materials appears in Table I. Powder samples were prepared for experimental use by dissolving them in methylene chloride followed by solvent evaporation in glass petri dishes. An optically clear, microscopically smooth substrate is formed. To produce the nanoporous surface, the plastic substrates

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Supported by The Devices and Technology Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Contract #NOI-HV-8-2921.

TABLE I. MATERIAL EVALUATED

Plastic Material			
1.	Hytrel* polyester elastomer[+]	4056	pellets
2.		5556	pellets
3.		6346	pellets
4		7246	pellets
5.	Copel* silicone polycarbonate[#]	4330	powder
6.		3320	powder
7.		4020	cast sheet
8.		3320	cast sheet
9.		3320	extruded sheet
10.		MEM-213	cast sheet
11.		4020	extruded rod 2 mm Dia.
12.		3320	extruded rod 2 mm Dia.
13.	Lexan* polycarbonate[&]	104	sheet
14.		104	extruded rod 2 mm Dia.
15.	VITUF* polyethylene terephthalate[o]	VFR-5041	pellets
16.	Mylar*		sheet

*Reg. U.S. Pat. and TM office.
[+]Block copolymers of short-chain diol terephthalate and long-chain polyether diol terephthalate, DuPont.
[#]Poly (dimethyl siloxane) - bisphonel - a carbonate block copolymer, G.E.
[&]G.E.
[o]Goodyear Tire and Rubber Co.

were exposed to Californium-252, which produces spontaneous fission fragments. Nuclear particle bombardment was performed in a vacuum chamber. Substrate to source distance was 1.25 cm, 2.5 cm, 6.75 cm or 10 cm. Following bombardment the substrates were etched in 6.25 N sodium hydroxide with continuous agitation. Etching solution temperature varied between 35° and 70°C. Etching times from 15 mins to several hours were examined.

Precoating of the PAD with Autologous Cells. An important feature of the percutaneous access device is the coating of autologous fibroblasts and collagen on the neck of the device prior to implantation. This was accomplished by in vitro cell culture. Two problems relating to the development of this surface, referred to as the "autologous living collagen-coated nanoporous" (ALCON) surface,were examined in great detail. First, the optimal conditions for fibroblast growth and collagen deposition in vitro, were determined. Experiments were conducted using rat, dog and pig fibroblasts derived from the dermis of these respective animals. Two types of tissue culture media, MEM (Earle's Base) and F12 (K.C. Biological), were tested. The growth stimulants tested included Fibroblast Growth Factor (FGF, 12.5 ng-100 ng/ml), Epidermal Growth Factor (EGF, 1 ng-20 ng/ml), Endothelial Cell Growth Supplement (ECGS, 100 μg/ml-200 μg/ml), Multiplication Stimulating Activity (MSA, 67 ng/ml), and Histamine (0.5 mg-3.0 mg/ml) (all growth factors from Collaborative Research, Inc.). The collagen stimulants tested were ascorbic acid (50 μg/ml), α-ketoglutaric acid (100 μg/ml) and iron sulfate (1 μg/ml). Ascorbic acid was added to the cultures daily; all other stimulants were incorporated into the culture media. Cell growth analysis was performed with a Coulter Counter. Collagen deposition in cell cultures was evaluated by the use of a Tibor-Pop silver impregnation staining technique and transmission electron microscopy.

Second, the most effective porous materials which could serve as supporting substrates for fibroblast cultures were determined. Experimental plastic substrates were sterilized and seeded with rat, dog, or pig fibroblasts. Some plastic substrates were pretreated with Human Fibronectin (HFN, Collaborative Research, Inc.) prior to seeding.

RESULTS AND DISCUSSION

Relief of Mechanical Stress. Figure 4 shows the average and standard deviation of strain obtained during stretching and compression after a sham implant. The strain is nearly uniform, which is what we would expect. The slight reduction in the center (over position ∅ mm) is probably due to reinforcement of the region by scar tissue. Figure 5 shows the same plot for a 100 mm implant. Note the substantial reduction in strain over the central portion of the implant (from +20 to -50 mm on the position scale, implant probably is not centered exactly under the tattoo grid). Such reduction in strain, however, was not always present. The plot shown in Figure 6 is indistinguishable from controls.

We believe (pathology results are not yet available) that this variability in our results is due to unintentional variation in implantation technique. When all of the hypodermis is successfully removed and the flange is in direct contact with the dermis, results such as Figure 5 are obtained. However, when even a thin layer of subcutaneous fat is left, local skin reinforcement and strain redistribution is either diminished or absent.

Figure 7 shows cross sections through the implant with the surrounding tissues. These implants were retrieved from a preliminary series of animals used to develop implantation technique. Section L3 shows a flange implanted within the dermis. A thin layer of scar tissue surrounds the implant and scar tissue from a fixation suture may be seen in the upper left hand corner. Flanges placed in this position were firmly bound to the surrounding tissue. Scanning electron micrographs of the flange-tissue interface showed that the dacron velour fibersss of the flange had become tortuously intertwined with the surrounding tissue. Section L4 shows a flange implanted just beneath the dermis with a thin layer of subcutaneous fat separating the implant from the dermal layer. No apparent disruption of the surrounding tissue has occurred as a result of the flange presence.

The pig, though its skin is similar to that of the human, is not an ideal model. The subcutaneous fat layer can be over 6 cm thick, and the dermis is also considerably thicker than that of humans. In the preliminary experiments, when all the hypodermis was thoroughly removed, necrosis over the implant site was a frequent complication. Therefore, in the present series of experiments, more care was taken to avoid damaging the dermis, and apparently some hypodermis was left in place.

Whether the human skin is less prone to necrosis and implantation can be carried out more consistently, we do not yet know. If the same problems persist or can be expected clinically, an alteration of the PAD design will be necessary. In conjunction with the use of a flange the PAD neck will likely be made of a material (Silicone-polycarbonate 4020) with mechanical properties similar to that of skin. This would provide additional stress attenuation at the tissue-device interface.

The Nanoporous Surface. Plastics #5 - #14 (Table I) were found to be suitable materials for nuclear particle tracks formation. The parameters which control the density and size of particle track have been defined. Particle track density was controlled directly by adjustments in exposure time according to the following formula:

$$\text{time (secs)} = \frac{\text{track density (pores/cm}^2\text{) x substrate area (cm}^2\text{)}}{\text{source emission rate (particles/sec) x efficiency (pores/particle)}}$$

Particle track size was controlled by etching temperature (higher temperatures produce faster etching) and etching time (longer etching times produced larger pores)[5]. It was found that only if temperatures of around 40-50°C and freshly prepared etching solution were utilized, pores of less than one μm diameter having a considerable depth (10-20 μm) could be produced. Lower temperatures resulted in minimal etching and higher temperatures produced shallower pores.

Precoating of the PAD with Autologous Cells. Optimal conditions for fibroblast growth and collagen deposition were similar for dog, pig and rat cells. Minimum Essential Media (MEM, K. C. Biological, Inc.) was the most effective media for fibroblast growth. Of the numerous growth stimulant additives tested, Fibroblast Growth Factor (FGF) and Endothelial Cell Growth Supplement (ECGS) (both from Collaborative Research, Inc.) were found to be extremely effective in promoting increased cell growth. A growth rate increase of as much as 6 times the normal rate was observed when a combination of these 2 additives was used. For collagen production to occur in vitro, it was essential to add ascorbic acid to the culture media. α-Ketoglutaric acid and $FeSO_4$ further improved collagen production, though neither was essential. Significant amounts of collagen were observed in fibroblast cultures by light microscopy and electron microscopy following extended treatment of cells with these additives (2 wks). Plastic substrates acceptable for nuclear track formation were also found effective as cell growth substrates. A dramatic increase in cell growth on these plastics was achieved by pretreating them with Human Fibronectin (HFN) (Collaborative Research, Inc.) before seeding them with cells (Figure 8).

CONCLUSION

The ground work has now been laid for the development of this percutaneous access device. The feasibility of creating the autologous living collagen-coated nanoporous surface appears inherent from the results achieved to date. Protection of the ultimate tissue-implant seal in vivo by use of a subdermal flange in conjunction with a deformable neck appears promising. At the present time, ALCON surface is being evaluated in vitro. No flaws in the PAD design reasoning have been encountered to date.

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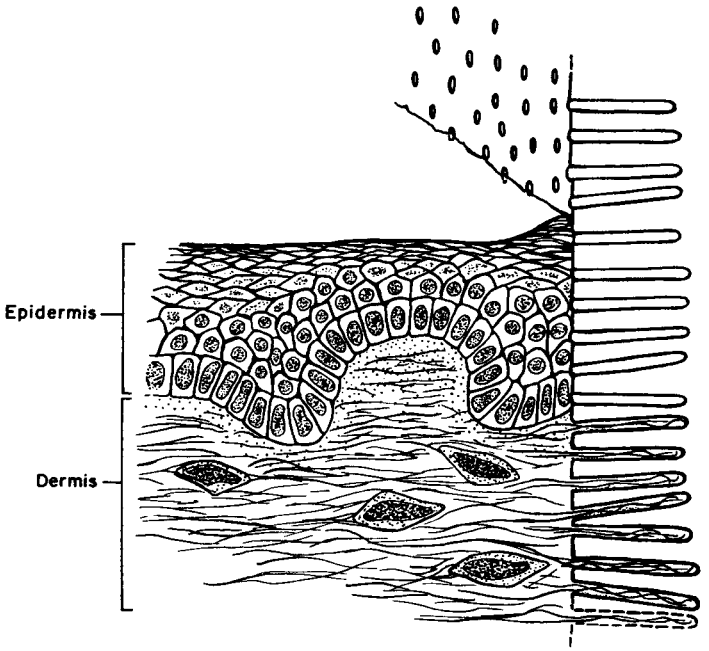

Figure 1. Schematic representation of tissue-device interface showing collagen interlocking with the porous implant surface. Basal cells are prevented from channeling between the tissue and the device. (Drawing not to scale; elements of skin not essential to illustrating proposed concept are not shown.)

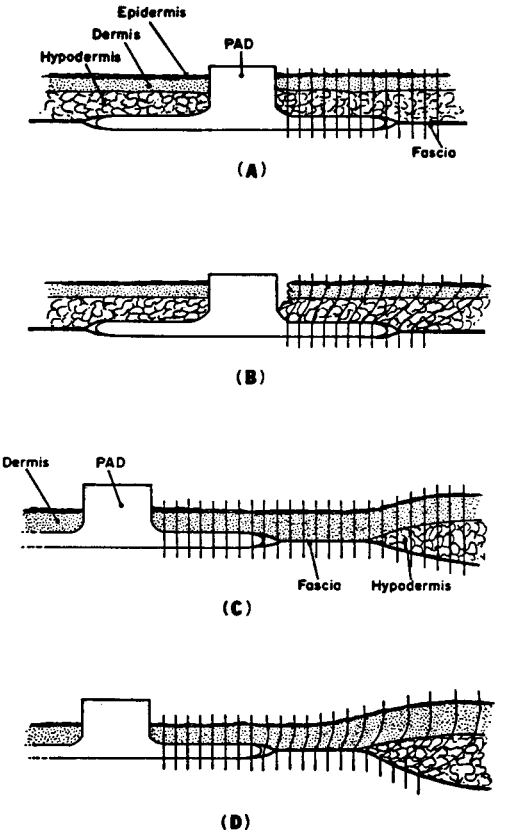

Figure 2. Schematic view of PAD with large flange implanted in soft tissue. (A) Resting state. Imaginary grid marks are vertical, indicating that no forces are being applied to the region containing the PAD. (B) Force has been applied. Grid marks indicate displacement pattern. Because of fixation technique, displacement is maximal in vicinity of PAD neck, and tear results. (C) Schematic diagram of PAD implanted according to proposed technique. Resting state. (D) In response to applied force, strain is maximal at outer margin and beyond PAD, while strain in region of PAD neck remains minimal, as in (C).

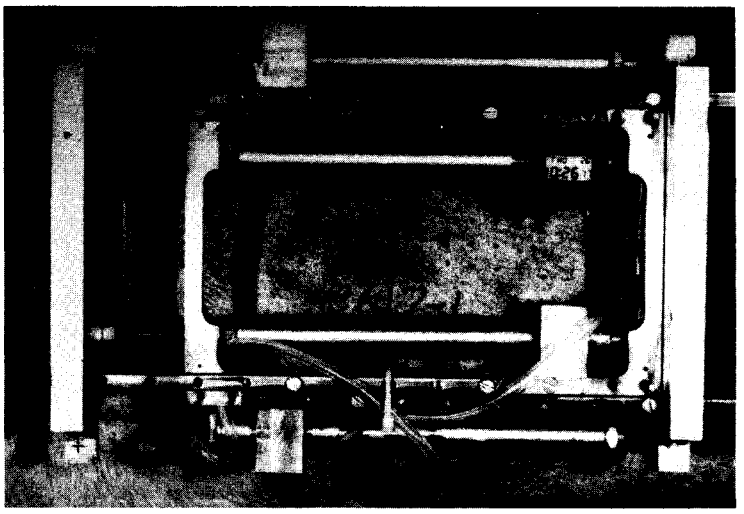

Figure 3. Device in resting state attached to pig skin. Note tattoo marks used to visualize skin deflection.

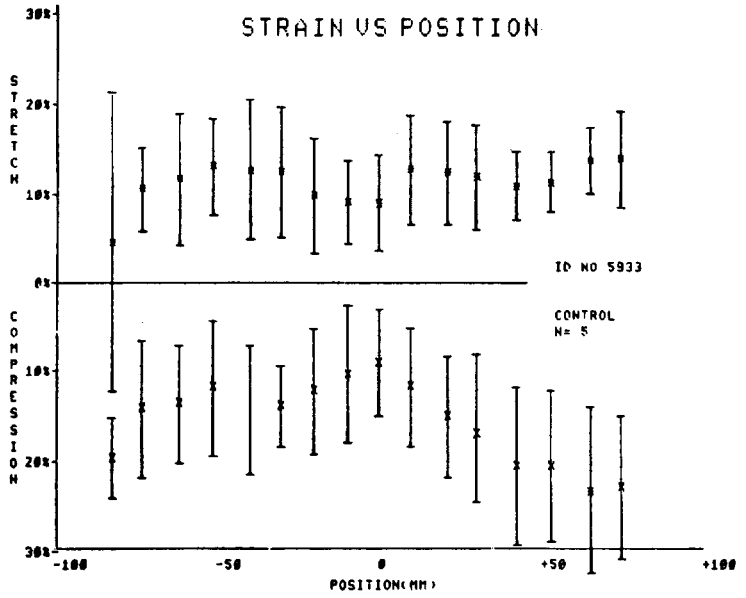

Figure 4. Average and standard deviation of strain vs position over site of implant (sham operation).

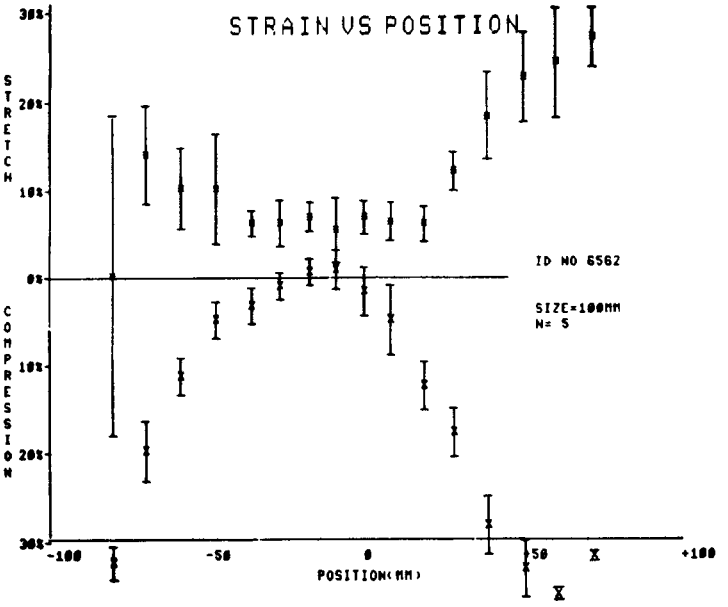

Figure 5. Average and standard deviation of strain vs position over site of implant (100 mm).

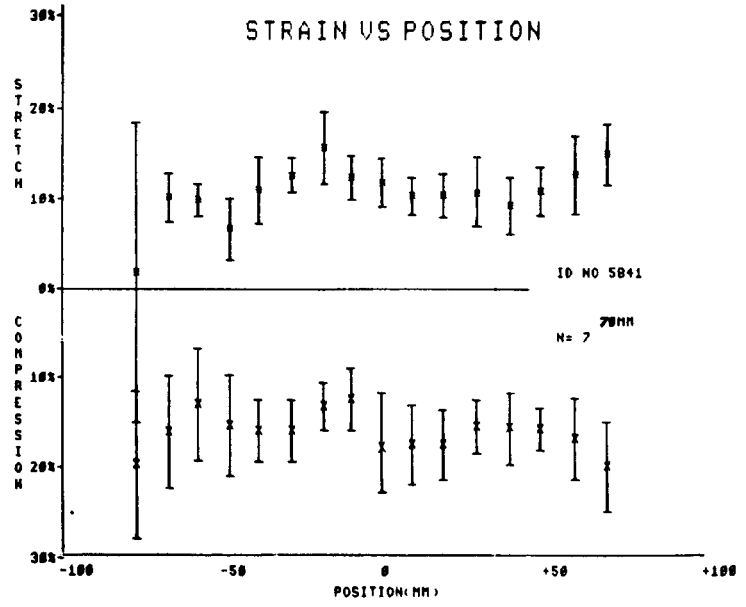

Figure 6. Average and standard deviation of strain vs position over site of implant (70 mm).

Figure 7. Pathological preparation of implant and surrounding tissue. Components include (top to bottom) the epidermis, dermis, implant surrounded by small amount of scar tissue, subcutaneous fat and muscle layers.

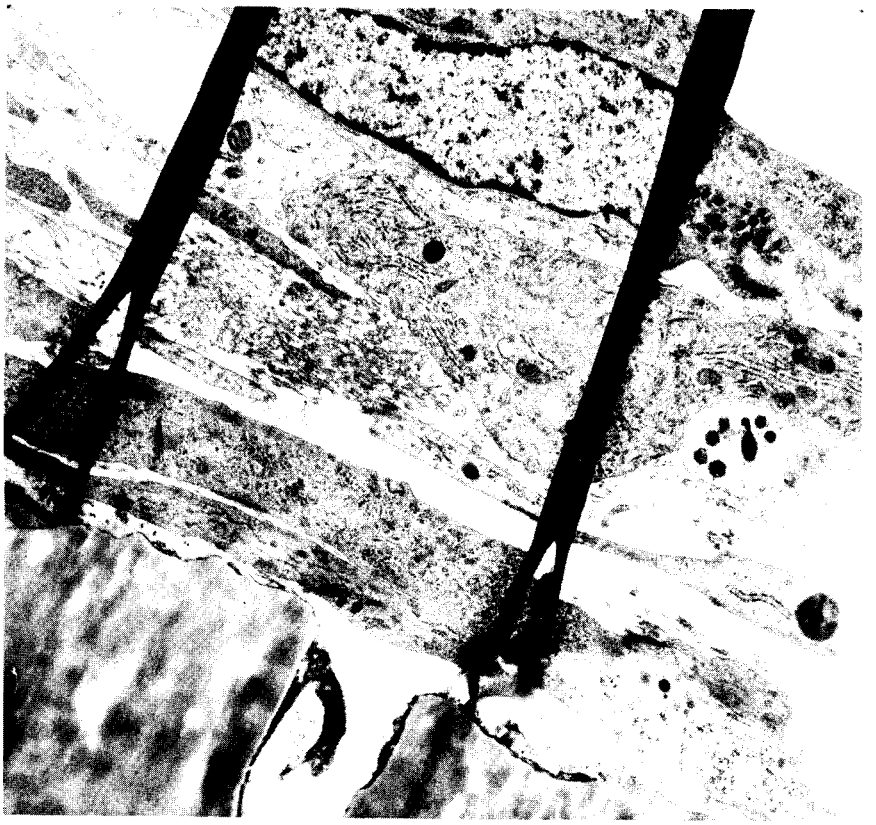

Figure 8. Electron micrograph showing rat fibroblasts growing on Lexan. Several cell layers may be seen and collagen is present between the layers. The surface of the Lexan was pretreated with Human Fibronectin and a thin coating may be seen on its surface. The fibroblasts are overlying a one μm pore. 20,000X.